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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/701,007	ALLERSON ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,5,34,37,38,49,50,53-63,72,74-78,94-96,104 and 105* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,5,34,37,38,49,50,53-63,72,74-78,94-96,104 and 105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 2-14-08.

Claims 4, 5, 34, 37, 38, 49, 50, 53-63, 72, 74-78, 94-96, 104 and 105 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2-14-08 has been entered.

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 4, 5, 34, 37, 38, 49, 50, 53-63, 72, 74-78, 94-96, 104 and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al (EMBO J., vol. 20, No. 23, pages 6877-6888, 2001), Fosnaugh et al (US 2003/0143732) and

Morrissey et al (US 2003/0206887) in view of the combined teachings of Arnold et al (USPN 6,262,036), Damha et al (US 2005/0142535) and McKay et al (USPN 6,133,246) for the reasons of record set forth in the Office action mailed 9-14-07.

Applicant's arguments filed 2-14-08 have been fully considered but they are not persuasive. Applicant argues that the instant invention would not have been obvious to one of ordinary skill in the art because nothing in the teachings of Elbashir, Fosnaugh, Morrissey, Arnold, Damha or McKay, collectively or individually, suggest that the particular pattern of chemical modifications recited in the claims would have been any more desirable or useful than any of the other possible patterns of chemical modifications encompassed by the prior arts' descriptions of chemical modifications. Applicant argues, for instance, that the references of Elbashir, Fosnaugh and Morrissey do not provide any guidance or detail regarding the particular types of chemical modifications, the number of chemical modifications, and the positioning of the chemical modifications within an siRNA molecule that would have been expected to impart beneficial properties while still maintaining the molecule's activity. Applicant asserts that the teachings of the cited references instead teach away from the claimed pattern of chemical modifications by illustrating particular chemically modified siRNA molecules that are very different from those recited in the claims, and Elbashir teaches away from the claimed pattern of chemical modifications by describing siRNA duplexes that contain chemical modifications at locations that vary significantly from the pattern claimed, and that do not enhance the molecules' activities or properties. Applicant additionally argues that Elbashir, Fosnaugh, Morrissey, Arnold, Damha and McKay fail to teach or

suggest first and second oligomeric compounds having the instantly claimed pattern(s) of chemical modifications, and instead merely provide generalized teachings regarding chemical modifications of RNA, or describe oligomeric compounds that have patterns of chemical modifications that differ significantly from the pattern(s) instantly claimed. Applicant asserts that the combined references do not provide guidance regarding specific patterns of 2' chemical modifications that would be expected to enhance siRNA properties or activities.

Contrary to Applicant's assertions, the combination of references, relying on the teachings of Elbashir, Fosnaugh and Morrissey et al in view of the combined teachings of Arnold, Damha and McKay, indeed render the instant invention obvious for the reasons set forth below.

The effect of various arrangements of different modifications on siRNA's ability to bind to and inhibit target gene expression in the presence of RISC was taught previously in the art, including Fosnaugh, whose modified siRNAs included 2'-fluoro or methoxyalkyl groups of various alkyl chain lengths, and which oligonucleotides optionally further comprised, in addition to various 2'-substituent containing motifs, internucleotide linkage modifications comprising phosphorothioate internucleotide linkages, 3'-and/or 5'-terminal caps and terminal, inverted deoxyabasic. The effect of different arrangements of these modifications on siRNA ability to bind to and inhibit target gene expression in the presence of RISC was taught previously by Fosnaugh.

The distinctions between antisense mediated gene inhibition and siRNA mediated gene silencing have been taught previously by many in the art. Elbashir, for

instance, describes in the introduction (pages 6877-8) the various studies that had been underway to determine the mechanisms and enzymes involved in siRNA mediated cleavage. No assumptions existed in the art at the time of the instant invention that the same configurations that were optimal for RNAse H activity (e.g. as described in Damha) are applicable to siRNA and the respective endonucleases involved in siRNA mediated inhibition. So, contrary to Applicant's assertions, in the absence of this assumption, there is no teaching away offered by the teachings of Damha. Furthermore, Elbashir taught a correlation between the placement of 2'-substitutions on siRNA oligonucleotides and the retention of siRNA activity - with no mention of any correlation between the enzymes involved in siRNA gene silencing and those involving antisense and RNAse H.

Contrary to Applicant's assertions, Elbashir, Fosnaugh and Morrissey taught the routine experimentation involved in designing and testing arrangements of modified residues on siRNA for their ability to inhibit target gene expression. All of the instantly claimed modifications were well known in the art, and researchers in the art routinely assayed different configurations of modifications for antisense, ribozyme and siRNA mediated inhibition.

An alternating motif would have been a logical configuration or design choice to incorporate into siRNA molecules, and testing the effect of such a well known configuration would have involved routine experimentation at the time of the instant invention.

McKay taught numerous motifs and combinations of modified residues within antisense oligonucleotides, including the incorporation of 2'-modified sugars which include 2'-fluoro, 2'-bromo, 2'-O-alkyl groups, modified nucleobases, modified internucleotide linkages, 2'-β-D-deoxynucleosides and combinations thereof, as well as the optimization of modifications for maximizing target binding, cellular uptake and oligonucleotide stability (see esp. col. 7-12; Tables 4-26, esp. Tables 11 and 12, and Table 26).

McKay is relied upon in the instant 103 rejection for teaching various combinations of modified residues incorporated into antisense oligonucleotides, including 2'-modified nucleosides which include the incorporation of 2'-fluoro, 2'-bromo, 2'-O-alkyl groups, as well as the incorporation of modified nucleobases, internucleotide linkages, 2'-β-D-deoxynucleosides, and combinations thereof. McKay is therefore properly relied upon for the routine experimentation of incorporating these well known modifications into various motifs, and is relied upon for teaching the well known effects of these modifications, including enhancing target binding, cellular uptake and oligonucleotide stability.

Fosnaugh and Morrissey both taught effects on gene silencing activity after incorporating various motifs and configurations of 2'-modifications into siRNA molecules, including the incorporation of fluoro or methoxyalkyl groups of various alkyl chain lengths, and which oligonucleotides optionally further comprised phosphorothioate internucleotide linkage modifications, 3'-and/or 5'-terminal caps, and inverted deoxyabasic terminal moieties. Fosnaugh and Morrissey taught the routine

experimentation involved in testing the effects of different arrangements of these various, well known modifications on siRNA's ability to bind to and inhibit target gene expression in the presence of RISC. Fosnaugh and Morrissey also are relied upon for teaching compositions comprising modified and unmodified siRNAs (and RISC) for target gene inhibition.

Damha taught alternating 2'-β-D-deoxynucleosides with 2'-modified nucleosides in inhibitory oligonucleotides, and the effects of this configuration on various properties of inhibitory oligonucleotides, including effects on target binding by antisense molecules and their inhibition of target gene expression. Damha taught the effects of various motifs or configurations of modified residues on the antisense oligonucleotides' abilities to inhibit target expression, particularly on their ability to elicit RNAse H cleavage of a target strand.

Applicant is correct that Elbashir teaches in the abstract that "[s]ubstitution of one or both siRNA strands by 2'-deoxy or 2'-O-methyl oligonucleotides abolished RNAi, although multiple 2'-deoxynucleotide substitutions at the 3' end of siRNAs were tolerated." However, a further reading of Elbashir clarifies the effect of these modifications on siRNA activity. In the bridging paragraph between pages 6881-6882, Elbashir teaches that substitution of 8 out of 42 nuceotides of the siRNA duplex did not lead to loss of activity, and that SiRNA with 2'-deoxynucleotides produced "significantly active siRNAs". This is in contrast to complete substitution of one or both siRNA strands with either 2'-O-methyl or 2'-deoxy residues, which led to abolition of RNAi activity. And on page 6884, second full paragraph, some of the "most efficient siRNA

duplexes" included 2'-deoxy modifications. So, contrary to Applicant's assertions, only the complete substitution of the strands with these modifications lead abolished activity.

Applicant is correct that Arnold does not teach alternating ribonucleosides and β-D-deoxyribonucleosides *per se*. But, contrary to Applicant's assertions, both Arnold and Damha taught the well known motif of alternating 2'-β-D-deoxynucleosides with 2'-modified nucleosides in oligonucleotides for enhancing target binding and stability. Arnold taught inhibitory oligonucleotides comprising 2-β-D-deoxynucleosides and 2'-modified nucleosides, and the introduction of these modifications into inhibitory oligonucleotides for enhancing their target binding ability and their stability, also comparing the inhibitory capabilities in the presence of modified and unmodified internucleotide linkages. Arnold taught antisense oligonucleotides comprising alternating 2'-β-D-deoxynucleosides with 2'-modified nucleosides, and the introduction of these modifications for enhancing target binding stability (see esp. example 34, col. 48-50).

Morrissey taught various ways of designing and optimizing 2'-O-modifications on siRNA, including fluoro or methoxyalkyl groups of various alkyl chain lengths, inverted abasic termini, and 5' and 3' capped termini. Morrissey taught the effect of various motifs or arrangements of 2'substitutuents and modified phosphorothioate internucleotide linkages on target gene inhibition by siRNA in compositions further comprising RISC.

So, contrary to Applicant's assertions, the motif comprising alternating 2'-β-D-deoxynucleosides with 2'-modified nucleosides was well known in the art, the testing of

various configurations of the modifications claimed on siRNA activity required routine experimentation well known in the art. And the teachings of Elbashir, Fosnaugh, Morrissey, Arnold, Damha and McKay, regarding the advantages of modifying oligonucleotides to enhance stability and target binding, while retaining siRNA or antisense activity, actually provide a reasonable expectation of success of finding the instantly claimed design choice of modified oligonucleotides which retain siRNA activity, and therefore render the instant invention obvious.

Elbashir taught methods of target gene inhibition in embryo lysates comprising siRNA molecules comprising 2'-deoxy and 2'-O-methyl substitutions. Elbashir et al teach a correlation between the placement of 2'-substitutions on the oligonucleotides and the retention of siRNA activity (see esp. the abstract on p. 6877, fig. 8 and text on p. 6885).

Fosnaugh taught various motifs and configurations of 2'-modifications, including fluoro or methoxyalkyl groups of various alkyl chain lengths, phosphorothioate internucleotide linkage modifications, 3'-and/or 5'-terminal caps, terminal inverted deoxy abasic moieties, and the effect of arrangements of these different modifications on siRNA ability to bind to and inhibit target gene expression in the presence of RISC. Fosnaugh routinely compared the ability of modified and unmodified siRNAs to inhibit target gene expression in the presence of RISC.

Morrissey taught various ways of designing and optimizing 2'-O-modifications on siRNA, including fluoro or methoxyalkyl groups of various alkyl chain lengths, and abasic, inverted abasic termini and 5' and 3' capped termini, and the effect of various

motifs or arrangements of these 2'substitutuents and modified phosphorothioate internucleotide linkages on target gene inhibition by siRNA in compositions further comprising RISC (see fig. 4 and 5, page 1, right col., p. 6, right col., p. 9, p. 20-21, claims 20-25).

So, contrary to Applicant's assertions, Elbashir, Fosnaugh and Morrissey all taught the designing and testing of various arrangements of modified residues on siRNA for their ability to inhibit target gene expression - using routine experimentation for both the incorporation of these well known modifications, and assaying different configurations for siRNA mediated inhibition. One of ordinary skill in the art would have incorporated 2'-β-D-deoxynucleosides and 2'-modified nucleosides into siRNA molecules because these modifications were well known in the art at the time of the instant invention. An alternating motif would have been a logical configuration or design choice to incorporate into and siRNA molecule, and testing the effect of such a well known configuration would have involved routine experimentation at the time of the instant invention.

For these reasons, the instant invention as a whole would have been *prima facie* obvious to one of ordinary skill at the time it was made.

Claims 4, 5, 34, 37, 38, 49, 50, 53-63, 72, 74-78, 94-96, 104 and 105 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 36, 40, 44, 46-49, 52-64, 74-80, 93, 98-100 and 104

of copending Application No. 10/860,265 for the reasons of record set forth in the Office action mailed 9-14-07.

No arguments were made addressing this rejection.

Claims 4, 5, 34, 37, 38, 49, 50, 53-63, 72, 74-78, 94-96, 104 and 105 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-24 of copending Application No. 11/054,848 for the reasons of record set forth in the Office action mailed 9-14-07.

No arguments were made addressing this rejection.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
3-21-08

/Jane Zara/

Primary Examiner, Art Unit 1635